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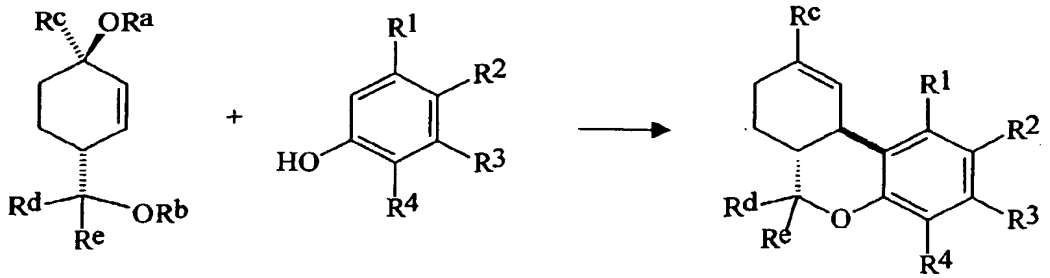
(54) Title: SYNTHESIS OF CANNABINOIDS



Compound (B) Compound (C) Compound (A)

(57) Abstract: The present invention relates to a process for the production of compound (A) comprising reacting compound (B) with compound (C). A further ring closure reaction may be necessary. The invention further relates to certain novel compounds of formula (B).

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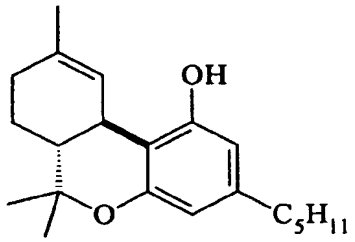
SYNTHESIS OF CANNABINOIDS

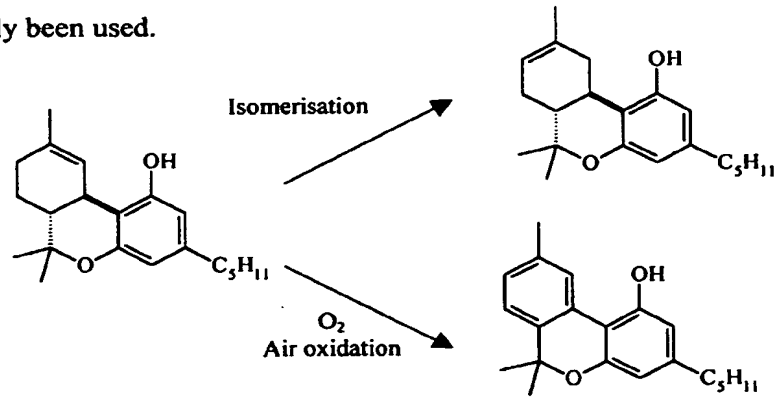
The present invention relates to a novel process that can be used to produce (-)-Δ^9-tetrahydrocannibinol and related cannibinoid compounds. The invention further relates to novel compounds used in the process.

(-)-Δ^9-Tetrahydrocannibinol (Δ^9-THC) is the active ingredient in marijuana. It is used therapeutically as an inhalant or an oral drug for stimulation of appetite among AIDS and cancer chemotherapy patients. Related cannibinoid compounds that show pharmacological activity are also known. In particular, there have been attempts to produce water soluble analogues of Δ^9-THC ('The Total Synthesis of Cannibinoids' in The Total Synthesis of Natural Products, Vol 4, John ApSimon, Wiley, 1981, pp 239-243).



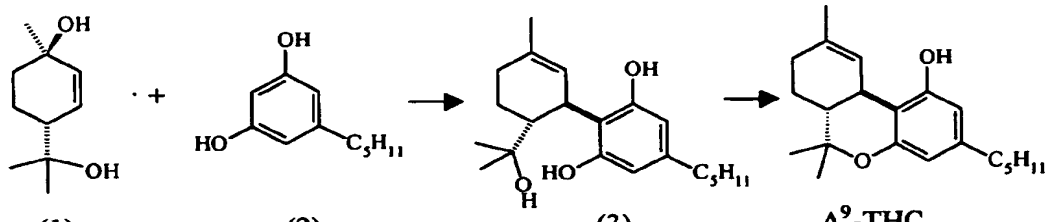
Δ^9-THC

The chemical synthesis and isolation of Δ^9-THC are both challenging. Δ^9-THC is a very high boiling, viscous liquid. It is very prone to acid-catalysed isomerization to the thermodynamically more stable Δ^8 isomer, it is easily oxidized by oxygen to inactive cannibinol, and it is sensitive to light and heat. All of these factors make purification difficult, especially on an industrial scale, and chromatography has generally been used.



Previous syntheses of Δ^9-THC have tended to be either lengthy or low-yielding. Most involve coupling of a chiral terpene to a resorcinol derivative. The primary difficulty has been lack of selectivity in the coupling. Acid catalysed couplings have generally led to mixtures of products (Crombie et al, J Chem Soc. Perkin Trans. I 1988 1243). Attempts to avoid the selectivity problem by using base-catalysed coupling reactions have involved lengthier syntheses overall (Rickards et al, J. Org. Chem. 1984 49 572). Syntheses not using chiral terpenes have yielded racemic product (Childers et al, J. Org. Chem. 1984 49 5276).

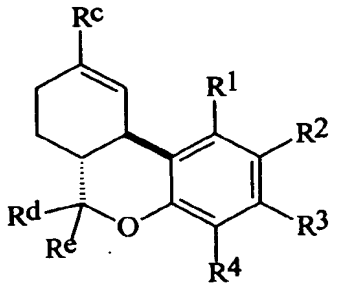
In seemingly the best known method (US 5,227,537), Stoss claims that acid-catalysed coupling of (+)-*p*-menth-2-ene-1,8-diol (1) with olivetol (2) can be stopped at the intermediate Friedel-Crafts product (3), and then the intermediate (3) can be isolated and converted in good yield to Δ^9-THC using $ZnBr_2$ (24 hours, refluxing CH_2Cl_2). The present inventors have encountered several problems with this scheme. The initial *p*-toluenesulfonic acid catalysed Friedel-Crafts reaction was difficult to stop cleanly at the intermediate (3) under Stoss' conditions and gave mixtures of the intermediate (3) and Δ^9-THC, the ring-closed product. Any Δ^9-THC formed is likely to isomerize to Δ^8-THC under the disclosed conditions. The use of a heavy metal such as $ZnBr_2$ in the last step of an industrial process is highly undesirable as it may lead to traces of metal in the product, and this is especially undesirable for pharmaceuticals. Stoss' method therefore appears to offer no real advantage in yield or purity of Δ^9-THC over a one-pot coupling that goes directly to Δ^9-THC. Razdan has published a one-pot method for coupling of (+)-*p*-menth-2-ene-1,8-diol (1) with olivetol (2) to produce Δ^9-THC (Razdan et al, Tet. Lett. 1983 24 3129). This also suffers from several problems: it uses nearly 14 equivalents of $ZnCl_2$ as the acid, and uses six equivalents of olivetol (2). Even under these conditions, the yield is still only 28% from (+)-*p*-menth-2-ene-1,8-diol (1).



(1) (2) (3) Δ^9-THC

Thus there is a need for a short, practical, high-yielding synthesis of Δ^9-THC that can be practised on an industrial scale. This is the problem that the present inventors have set out to address.

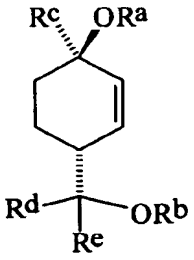
Accordingly the present invention provides a process for the production of a compound of general formula A:



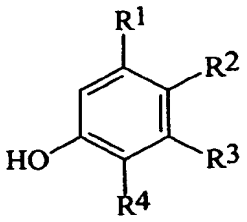
Compound A

wherein R^c, R^d and R^e are independently H, alkyl, or substituted alkyl; and R^1 to R^4 are independently H, OH, OR' (R' is alkyl, aryl, substituted alkyl or aryl, silyl, acyl, or phosphonate), alkyl, substituted alkyl, aryl, acyl, halide, amine, nitrate, sulphonate or phosphonate;

comprising reacting compound B with compound C:



Compound B



Compound C

wherein R^a is H, alkyl, aryl, acyl or silyl; R^b is alkyl, aryl or acyl; R^c, R^d, R^e and R^1 to R^4 are as hereinbefore defined;

and comprising, when necessary, a ring closure reaction.

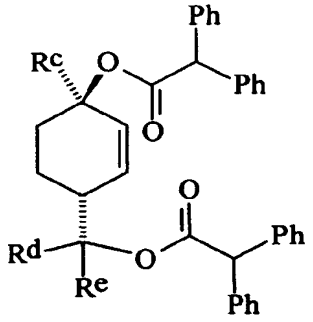
Preferably the reaction of compound B with compound C is carried out in the presence of an acid catalyst.

A substituted alkyl group may contain substituents such as halide, hydroxyl, amine and thiol. Alkyl groups may be saturated or unsaturated, acyclic or cyclic.

Compound B is similar to the (+)-*p*-menth-2-ene-1,8-diol used in the Stoss method. However, compound B is not a diol, and contains one or more ether or ester groups. R^b is alkyl, aryl or acyl, and preferably R^a is independently alkyl, aryl or acyl.

In a preferred embodiment, R^b is acyl, and OR^b is an ester group. Suitable ester groups include acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, *p*-nitrobenzoate, phthalate and succinate.

In an especially preferred embodiment both R^a and R^b are acyl groups so that compound B is a diester. The two ester groups are suitably chosen independently from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, *p*-nitrobenzoate, phthalate and succinate. An especially preferred compound has $OR^a = OR^b$ = diphenylacetate:



(4)

R^c, R^d and R^e can be varied independently of R^a and R^b and will affect the structure of the product, compound A. R^c is suitably Me or H, preferably Me. R^d and R^e are suitably Me or CH_2OH, preferably Me.

Compound C is a phenolic compound and is preferably a resorcinol derivative such as olivetol (3).

R^1 is preferably OR" wherein R" is H, alkyl, substituted alkyl, acyl or silyl. Most preferably R^1 is OH.

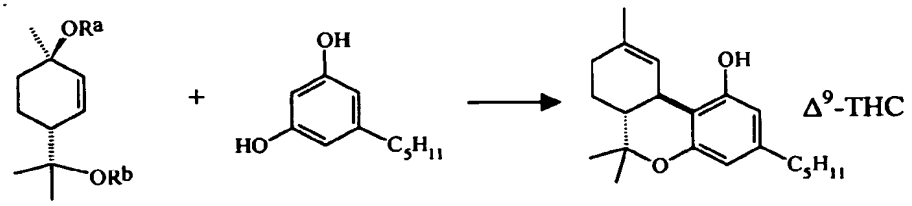
Preferably, R^2 and R^4 are H.

R^3 is suitably an alkyl group or substituted alkyl group. In a preferred embodiment, R^3 is C_5H_{11}. R^3 may contain groups that promote water solubility, eg ketone, ester, hydroxyl or amine groups. In one embodiment of the invention, R^3 contains a thioketal (this can be further converted to an aldehyde).

Most preferably, compound C is olivetol (3), wherein R^1 is OH, R^2 is H, R^3 is C_5H_{11} and R^4 is H.

Suitably, one equivalent of compound B is reacted with approximately one equivalent of compound C.

In a preferred embodiment of the invention compound B is an ether or ester of (+)-*p*-menth-2-ene-1,8-diol (R^c = Me, R^d = Me, R^e = Me), compound C is olivetol (R^1 = OH, R^2 = H, R^3 = C_5H_{11}, R^4 = H) and the product, compound A, is Δ^9-THC.

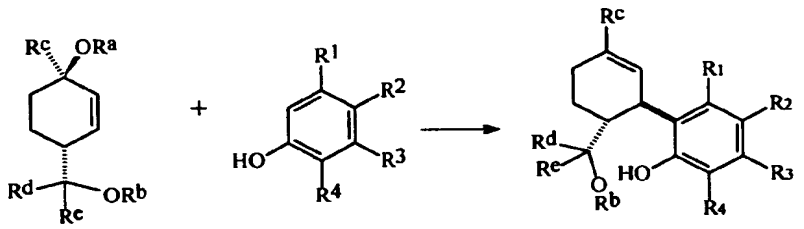


The present invention therefore provides a novel synthesis of Δ^9-THC.

The present invention provides both a one-step and a two-step process for the production of compound A. In the one-step process the reaction of compound B and compound C produces compound A directly. In the one-step process, suitably about

one equivalent of acid catalyst is used, eg between 0.8 to 1.5 equivalents. Preferably the reaction is carried out below 0°C, most preferably from –20°C to 0°C.

In the two-step process the reaction of compound B and compound C produces a ring-opened product, compound D:



B C Compound D

For the two-step process, suitably less than one equivalent of acid is used, preferably from 0.1 to 0.5 equivalents. Preferably the reaction is carried out below 0°C, more preferably below –10°C. A ring closure step is then carried out. Suitable reagents for the ring closure step include acids such as $BF_3.(OEt)_2$ or TsOH. One possible advantage of the two-step process is that if compound D is a crystalline solid, purification of the intermediate is straightforward and this may lead to higher purity in the final product, compound A.

The present invention provides one-step and two-step syntheses that can be used to produce Δ^9-THC. The syntheses show improved selectivity and yield compared to prior art methods. The amount of isomers generated is small and purification is simple. The phenolic reactant (compound C) is not used in excess. The process is suitable for scale-up to an industrial process.

Preferably the yield of the synthesis of Δ^9-THC is greater than 50%, more preferably the yield is greater than 75%. The process also provides high purity Δ^9-THC. Preferably Δ^9-THC is obtained in greater than 70% purity, more preferably greater than 90% purity. Methods known in the art can be used to further purify the products of the reaction.

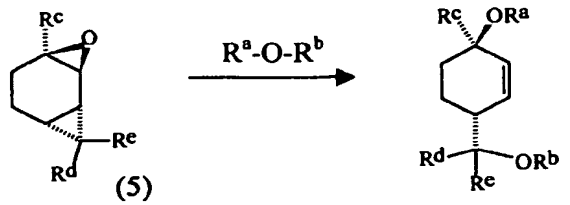
The process of the present invention is suitably carried out in a polar aprotic solvent, preferably methylene chloride.

Suitable acid catalysts include most Lewis acids. Non-metallic catalysts such as $BF_3.OEt_2$ and toluenesulfonic acid are preferred. Non-metallic catalysts offer advantages over the zinc catalysts used in the Stoss and Razdan methods because there is no possibility of a metal residue in the product. $BF_3.OEt_2$ is preferred because it is easily removed from the reaction mixture, and is less prone to causing isomerisation of Δ^9-THC to Δ^8-THC than *p*-TsOH. Suitably about one equivalent of catalyst or less is used, eg 0.1 to 1.5 equivalents. This offers a clear improvement over Razdan's method where 14 equivalents of acid are used.

Procedures for isolating the product, compound A, from the reaction mixture are well known to those in the art. Chromatography can be used to purify the product.

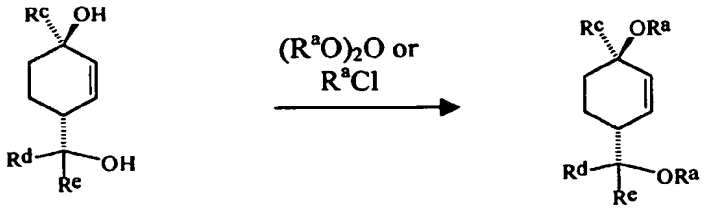
Certain compounds of structure B are novel and are particularly advantageous when used in the present invention. Compounds wherein both OR^a and OR^b are chosen independently from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, *p*-nitrobenzoate, phthalate and succinate (provided that only one of OR^a and OR^b is acetate) represent a further aspect of this invention. Preferably the groups are chosen so that compound B is a solid. Preferably both OR^a and OR^b are diphenylacetate. Preferably, R^c, R^d and R^e are Me.

Compound B can be produced by a variety of methods. Compounds wherein R^a = H or silyl can be prepared by the ring-opening of epoxides (5) with an alcohol, a carboxylic acid or silylated derivatives of alcohols and carboxylic acids. Reactions of this type are described in a co-pending patent application by the present inventors.



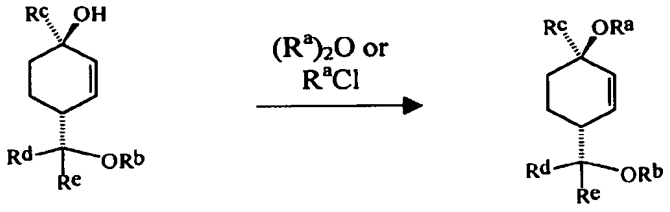
(5)

Compounds wherein R^a and R^b are both the same can be produced by base catalysed reaction of the corresponding diol (6) with anhydrides or chlorides.



(6)

Compounds wherein R^a is not H or silyl and wherein R^a and R^b are different can be produced by base-catalysed reaction of mono-ethers or mono-esters (7) with ethers or chlorides.



(7)

The following examples are illustrative but not limiting of the invention.

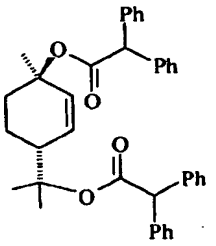
General Experimental Details

Anhydrous solvents were purchased from Aldrich Chemical Company (Milwaukee, WI, USA). Samples of Δ^9-THC and Δ^8-THC were obtained from RBI/Sigma (Natick, MA, USA). (+)-*p*-Menth-2-ene-1,8-diol was prepared as described in a co-pending patent application by the present inventors. TLC plates (silica gel GF, 250micron, 10 x 20cm) were purchased from Analtech (Newark, DE, USA). TLCs were visualized under short wave UV, and then by spraying with ceric ammonium nitrate/sulfuric acid and heating. Column chromatography was carried out using TLC grade silica gel purchased from Aldrich Chemical Company. NMR spectra were obtained on a Bruker 300 MHz instrument. HPLC area percentages reported here are not corrected. HPLCs were run on Shimadzu LC-10AD.

EXAMPLE 1a:

One-step reaction of bis(diphenylacetate) compound (4) with olivetol (3) to produce Δ^9-THC

Preparation of bis(diphenylacetate) compound (4)



(4)

A 25ml three-necked roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. Pyridine (12ml) was added and the pale yellow solution was stirred. Diphenylacetyl chloride (5.69g, 4.2eq.) was added. The solution turned brown. N,N-dimethylaminopyridine (0.1435g, 0.2eq.) was added. The mixture was stirred for 1 hour. (+)-*p*-Menth-2-ene-1,8-diol (1.00g) was added. The mixture became a lighter colour and solids precipitated. The slurry was allowed to stir overnight at room temperature. The reaction was quenched with water. The mixture was extracted three times with ethyl acetate. The organics were combined and washed with 2M HCl, saturated $NaHCO_3$, and saturated NaCl (aq.), dried over Na_2SO_4, filtered and concentrated *in vacuo* to orange oil. The oil was dissolved in hot methanol and cooled to crystallize. The white solid was collected and washed twice with cold methanol. After drying under vacuum, the yield was 3.282g (76.8% yield). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.4-7.2 (m, 20H), 5.89-5.84 (dd, 1H), 5.51-5.47 (dd, 1H), 4.90 (s, 2H), 2.7-2.6 (m, 1H), 2.0-1.9 (m, 2H), 1.7-1.6 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.35-1.2 (m, 1H). ^{13}C NMR: δ (ppm) 171.47, 171.44, 139.06, 138.84, 132.38, 128.64, 128.56, 128.51, 128.46, 128.28, 127.11, 127.07, 127.02, 85.12, 80.91, 58.32, 57.86, 44.22, 33.81, 25.41, 23.32, 22.81, 21.41. M.p. 111°C. Elemental Analysis: 81.66% C, 6.59% H. R_f (20% EtOAc/hexane): 0.54. $[\alpha]_D^{25}$ = +61.5° (c=1.00, $CHCl_3$). IR (KBr, cm^{-1}): 3061, 3028, 1720.5 (carbonyl stretch).

One-step reaction

A 25ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The bis(diphenylacetate) (4) (279mg, 0.499mmol) and olivetol (90mg) were added. Anhydrous CH_2Cl_2 (8ml) was added and stirred. The solution was cooled to –5°C internal temperature. $BF_3{\cdot}(OEt)_2$ (64µl, 1.0 eq.) was added. The solution gradually darkened to orange. After 30 minutes, the reaction was quenched with 10% Na_2CO_3 (10ml). The layers were separated and the organic layer was washed with 2 x 5ml 10% Na_2CO_3. The aqueous washes were combined and extracted twice with CH_2Cl_2. The organics were combined and washed with water and saturated NaCl solution, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to light yellow oil. The oil was chromatographed on 5g TLC mesh silica to yield 135.2mg (86.1%) of Δ^9-THC. NMR did show a small amount of solvent present. HPLC showed 96.6 area percent Δ^9-THC. ^1H NMR agreed with published reports and commercial samples. ^{13}C NMR ($CDCl_3$): δ (ppm) 154.81, 154.16, 142.82, 134.41, 123.74, 110.11, 107.54, 77.18, 45.83, 35.47, 33.58, 31.52, 31.17, 30.63, 27.58, 25.03, 23.34, 22.53, 19.28, 13.99. HPLC R.T.: 28.34min. R_f (10% MTBE/hexane): 0.30. $[\alpha]_D^{25}$ = -174.2° (c=1.16, EtOH).

EXAMPLE 1b:

Reaction of bis(diphenylacetate) (4) compound with olivetol to produce ring-open intermediate

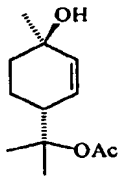
Bis(diphenylacetate) (4) was prepared as for example 1a.

A 25ml 2-neck roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. Bis(diphenylactetate) (4) (279mg, 0.499mmol) and olivetol (90mg) were added. Anhydrous CH_2Cl_2 (8ml) was added. The solution was stirred to dissolve the solids and then cooled to –20°C internal temperature. $BF_3{\cdot}(OEt)_2$ (16µl, 0.25eq.) was added. The solution was stirred for 12 minutes and then quenched with 10% Na_2CO_3 (aq.) (6ml). The mixture was extracted twice with CH_2Cl_2. The combined organics were washed with water and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to oil. Chromatography on 10g TLC mesh silica gel (2% MTBE/hexane – 15%) yielded Δ^9-THC (fractions 16-22, 31.4 mg, 20.0% yield),

but the predominant product was the diphenylacetate triol (the ring open product corresponding to compound D) (fr. 24-37, 160 mg, 60.7% yield). ^{1}H NMR ($CDCl_3$): δ (ppm) 7.26-71.8 (m, 10H), 6.26 (br s, 1H), 6.04 (br s, 1H), 5.35 (s, 1H), 4.51 (s, 1H), 3.92 (br d, 1H), 2.43-2.36 (m, 3H), 2.1-1.9 (m, 2H), 1.79 (m, 1H), 1.71 (s, 3H), 1.6-1.4 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.3-1.2 (m, 4H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$) δ ppm 171.56, 142.87, 139.24, 139.08, 128.64, 128.36, 128.31, 126.92, 126.89, 124.93, 115.43, 87.27, 57.53, 45.94, 35.43, 33.46, 31.51, 30.60, 29.96, 24.04, 23.34, 23.20, 23.17, 22.48, 13.97. R_f (20% EtOAc/hexane): 0.48. $[\alpha]_D^{25}$ = -45.9° (c=1.298, $CHCl_3$). Elemental Analysis: 78.69% C, 8.93% H.

EXAMPLE 2a:

One-step reaction of monoacetate compound (8) with olivetol to produce Δ^9-THC



(8)

A 25ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The monoacetate (8) (109mg) and olivetol (92.5mg) were added. Anhydrous CH_2Cl_2 (8ml) was added and stirred. The solution was cooled to –5°C internal temperature. $BF_3.(OEt)_2$ (65µl, 1.0eq.) was added. The solution gradually darkened to orange. After 24 minutes, the reaction was quenched with 10% Na_2CO_3. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The organics were combined and washed with water and saturated NaCl solution, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to oil. HPLC showed 64.0 area percent Δ^9-THC. The oil was chromatographed on 20g TLC mesh silica to yield 58.7mg (36.3%) of Δ^9-THC. ^{1}H NMR agreed with published reports and commercial samples.

EXAMPLE 2b:

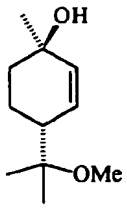
Reaction of monoacetate compound (8) with olivetol to produce ring-open intermediate

A 25ml 2-neck roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The monoacetate (8) (109mg, 0.514mmol) and olivetol (92.5mg) were added. Anhydrous CH_2Cl_2 (8ml) was added. The solution was stirred to dissolve the solids and then cooled to –20°C internal temperature. $BF_3{\cdot}(OEt)_2$ (16µl, 0.25eq.) was added. The solution was stirred for 45 minutes and then quenched with 10% Na_2CO_3 (aq.) (4ml). The mixture was extracted twice with CH_2Cl_2. The combined organics were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a colourless oil. Chromatography on silica gel yielded 90.5mg (47.0% yield) of acetyl triol (the ring open product corresponding to compound D). ^1H NMR ($CDCl_3$): δ (ppm) 6.22 (br m, 2H,), 5.76 (br s, 2H), 5.36 (s, 1H), 4.00 (br d, 1H), 2.67 (dt, 1H), 2.40 (t, 2H), 2.26-2.16 (m, 1H), 2.07-1.90 (m, 2H), 1.73 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.32-1.24 (m, 4H), 0.85 (t, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 170.83, 142.69, 138.03, 124.99, 115.42, 85.90, 44.29, 35.38, 33.47, 31.49, 30.66, 30.09, 25.16, 24.65, 23.17, 22.57, 22.43, 21.84, 13.95. R_f (20% EtOAc/hexane): 0.37.

EXAMPLE 3a:

One-step reaction of monomethoxy compound (9) with olivetol to produce Δ^9-THC

A 25ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and



(9)

cooled under N_2. The monomethoxy compound (9) (91.9mg) and olivetol (90mg) were added. Anhydrous CH_2Cl_2 (8ml) was added and stirred. The solution was cooled to –5°C internal temperature. $BF_3.(OEt)_2$ (16µl, 0.25eq.) was added. After 1 hour another 16µl was added. Two hours later, another 32µl was added. The solution gradually darkened to orange. TLC showed a mixture of Δ^9-THC and the ring open product, and

major spots. The reaction was quenched with 10% Na_2CO_3. The layers were separated and the organic was washed with water and sat. NaCl, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to oil.

EXAMPLE 3b:

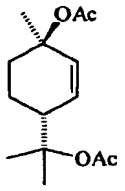
Reaction of monomethoxy compound with olivetol to produce ring-open intermediate

A 5ml roundbottom flask with a stir bar was oven-dried, fitted with a septum, and cooled under N_2. The monomethoxy compound (9) (33.5mg) in 1.5ml of anhydrous methylene chloride was added. Olivetol (32.7mg) and magnesium sulfate (134mg) were added. *p*-Toluenesulfonic acid monohydrate (34.6mg) was added. The slurry was stirred at room temperature for 30 minutes. Solid $NaHCO_3$ (100 mg) was added and stirred. The solids were removed by filtration. The solution was washed once with 5% $NaHCO_3$ (aq.). The aqueous wash was extracted once with CH_2Cl_2. The organics were combined, washed with water, and dried over Na_2SO_4. The solution was concentrated *in vacuo* and chromatographed on silica gel. Colourless oil of the methoxy triol (the ring open product corresponding to compound D) (35.3 mg, 56.0% yield) was obtained. ^1H NMR ($CDCl_3$): δ (ppm) 7.90 (br s, 1H), 6.68 (br s, 1H), 6.33-6.21 (br d, 2H) 5.75 (s, 1H), 3.74 (s, 1H), 3.20 (s, 3H), 2.44 (t, 2H), 2.07 (br s, 2H), 2.00-1.77 (m, 3H), 1.80 (s, 3H), 1.54 (m, 2H), 1.31 (m, 3H), 1.14 (s, 3H, 1.13 (s, 3H), 0.87 (t, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 186.50, 169.63, 166.85,143,41, 140.11, 123.58, 79.32, 48.63, 48.05, 35.51, 32.62, 31.52, 30.63, 27.76, 23.74, 23.01, 22.53, 21.95, 20.39, 13.99. Elemental Analysis: 73.3% C, 8.80% H. R_f (10% EtOAc/hexane): 0.25. $[\alpha]_D^{25} = -22.7°$ (c=0.088, $CHCl_3$).

EXAMPLE 4:

One-step reaction of diacetate (10) with olivetol to produce Δ^9-THC

Preparation of diacetate (10)



(10)

A 100ml three-necked roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. (+)-*p*-menth-2-ene-1,8-diol (10.00g) was added. Triethylamine (68.7ml, 8.4eq.) was added and the slurry was stirred. N,N-dimethylaminopyridine (1.435g, 0.2eq.) was added. Acetic anhydride (23.3ml) was placed in an addition funnel and added slowly over 15 minutes. The yellow solution became homogeneous. The solution was warmed to 35°C internal temperature and stirred for 2.5 hours, then raised to 40°C for another three hours, then allowed to stir for 13 hours at room temperature. The reaction was quenched with water while cooling in ice. The mixture was extracted three times with hexane and once with ethyl acetate. The organics were combined and washed with saturated NaCl (aq.), dried over Na_2SO_4, filtered and concentrated *in vacuo* to an orange oil. Chromatography on 50g TLC mesh silica yielded the diacetate (10) as a colourless oil (12.3g, 82.3%). The oil was cooled in dry ice to freeze the oil and then the solid was broken up with a spatula. It was allowed to warm to room temperature and it remained a white solid. ^1H NMR ($CDCl_3$): δ (ppm): 5.84 (dd, 1H), 5.54 (dd, 1H), 2.70 (m, 1H), 2.05-1.8 (m, 3H), 1.85 (s, 6H), 1.68 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) 169.95, 169.89, 132.40, 127.88, 83.79, 79.73, 43.62, 33.85, 25.26, 23.10, 22.74, 22.05, 21.49. m.p. 28-31°C. Elemental Analysis: 65.26% C, 8.61% H. R_f (20% EtOAc/hexane): 0.52. $[\alpha]_D^{25} = +73.5°$ (c=0.99, $CHCl_3$).

One-step Reaction

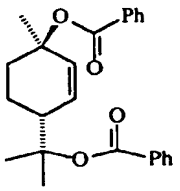
A 25ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The diacetate (10) (126.9mg, 0.499mmol) and olivetol (90mg, 0.499mmol) were added. Anhydrous CH_2Cl_2 (8ml) was added and stirred.

The solution was cooled to –5°C internal temperature. $BF_3.(OEt)_2$ (64µl, 1.0eq.) was added. The solution gradually darkened to red. After 15 minutes, the reaction was quenched with 10% Na_2CO_3. The layers were separated and the organic layer was washed with 10% Na_2CO_3. The combined aqueous were extracted once with CH_2Cl_2. The organics were combined and washed with water and saturated NaCl solution, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to a tannish oil (0.132mg). HPLC showed 88.8 area percent Δ^9-THC. Chromatography on silica gel yielded 95.9mg (61.0% yield) of Δ^9-THC. HPLC showed 94.9 area percent Δ^9-THC.

EXAMPLE 5:

One-step reaction of dibenzoate (11) with olivetol to produce Δ^9-THC

Preparation of dibenzoate (11)



(11)

A 25ml three-necked roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. (+)-*p*-Menth-2-ene-1,8-diol (1.00g) was added. Pyridine (6ml, 12.6eq.) was added and the pale yellow solution was stirred. N,N-dimethylaminopyridine (0.1435g, 0.2eq.) was added. Benzoyl chloride (2.73ml, 4eq.) was added. After 10 minutes, a solid precipitated. The slurry was allowed to stir overnight at room temperature. The reaction was quenched with water. The mixture was extracted three times with CH_2Cl_2. The organics were combined and washed with water and saturated NaCl (aq.), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The oil was chromatographed on 25g TLC mesh silica to yield a colourless oil. The oil was cooled in dry ice and froze, but melted on warming to room temperature. ^1H NMR($CDCl_3$) δ (ppm): 8.0 (dt, 4H), 7.51 (m, 2H), 7.40 (dt, 4H), 6.16 (dd, 1H), 5.88 (dd, 1H), 3.00 (m, 1H), 2.29 (m, 2H), 2.02 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.25 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 165.53, 132. 80, 132.53, 132.50, 131.77, 131.63, 129.40, 129.36, 128.39, 128.22, 128.16, 80.64, 44.55, 34.09, 25.81,

23.50, 23.10, 22.59, 21.99, 14.14, 14.05. Elemental Analysis: 76.21% C, 6.97% H. R_f (20% EtOAc/hexane): 0.57.

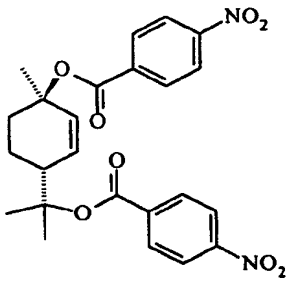
One-step Reaction

A 25ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The dibenzoate (11) (189mg, 0.499mmol) and olivetol (90mg) were added. Anhydrous CH_2Cl_2 (8ml) was added and stirred. The solution was cooled to –5°C internal temperature. $BF_3.(OEt)_2$ (64µl, 1.0eq.) was added. The solution gradually darkened to red. After 15 minutes, the reaction was quenched with 10% Na_2CO_3. The layers were separated and the organic layer was washed with water and saturated NaCl solution, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to oil. HPLC showed 78.8 area percent Δ^9-THC.

EXAMPLE 6:

One-step reaction of di-*p*-nitrobenzoate (12) with olivetol to produce Δ^9-THC

Preparation of di-*p*-nitrobenzoate (12)



(12)

A 25ml three-necked roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. (+)-*p*-Menth-2-ene-1,8-diol (1.00g) was added. Pyridine (6ml, 12.6eq.) was added and the pale yellow solution was stirred. N,N-dimethylaminopyridine (0.1435g, 0.2eq.) was added. *p*-Nitrobenzoyl chloride (4.58ml, 4.2eq.) was added. After a few minutes, tan solid precipitated. More pyridine (12ml) was added. The slurry was allowed to stir overnight at room temperature. The reaction was quenched with water. The mixture was extracted three times with ethyl acetate. The organics were combined and washed twice with saturated NaCl (aq.), dried over Na_2SO_4, filtered and concentrated *in vacuo* to light yellow solid. The solid was

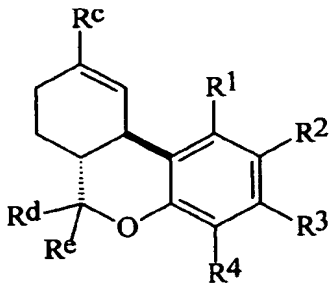
recystallized from isopropyl alcohol and dried under vacuum. The yield was 3.303g (120% yield), which clearly still contained pyridine and isopropyl alcohol by NMR. It was dried more and then recrystallized from ethyl acetate/hexane to give a lightly coloured solid (1.89 g, 68.7%). ^{1}H NMR (d_6-acetone) still seemed to have too many aryl protons. ^{1}H NMR (CD_2Cl_2) δ (ppm): 8.3-8.2 (m, 4H), 8.2-8.1 (m, 4H), 6.14 (dd, 1H), 5.88 (d, 1H), 3.04 (m,1H), 2.29 (m, 2H), 2.00 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H0, 1.67-1.65 (m, 2H). ^{13}C NMR (CD_2Cl_2) δ (ppm): 164.275, 164.244, 151.00, 133.00, 131.46, 131.09, 131.04, 129.29, 124.00, 123.96, 87.04, 82.75, 45.00, 34.55, 26.10. 23.83, 23.45, 22.64. m.p >200°C (decomposition). Elemental Analysis: 59.68% C, 4.71% H, 6.07% N. R_f (20% EtOAc/hexane): 0.41. $[\alpha]_D^{25}$ = +38.0° (c=0.21, $CHCl_3$).

One-step Reaction

A 10ml roundbottom flask with a stir bar was oven-dried, fitted with septa, and cooled under N_2. The di-*p*-nitrobenzoate (12) (116.5mg) and olivetol (45mg) were added. Anhydrous CH_2Cl_2 (4ml) was added and stirred. The solution was cooled to –5°C internal temperature. $BF_3.(OEt)_2$ (32µl, 1.0eq.) was added. The cloudy solution gradually darkened to orange. After 2 hours, the reaction was quenched with 10% Na_2CO_3. The layers were separated and the organic layer was washed with water and sat. NaCl, then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yellow oil. HPLC showed 71.5 area percent Δ^9-THC.

CLAIMS

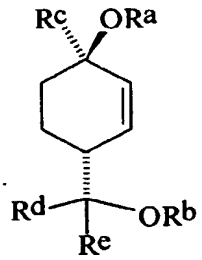
1. Accordingly the present invention provides a process for the production of a compound of general formula A:



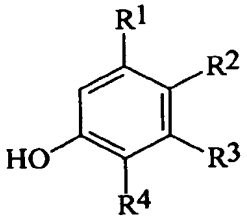
Compound A

wherein R^c, R^d and R^e are independently H, alkyl, or substituted alkyl; and R^1 to R^4 are independently H, OH, OR' (R' is alkyl, aryl, substituted alkyl or aryl, silyl, acyl, or phosphonate), alkyl, substituted alkyl, aryl, acyl, halide, amine, nitrate, sulphonate or phosphonate;

comprising reacting compound B with compound C:



Compound B



Compound C

wherein R^a is H, alkyl, aryl, acyl or silyl; R^b is alkyl, aryl or acyl; R^c, R^d, R^e and R^1 to R^4 are as hereinbefore defined;

and comprising, when necessary, a ring closure reaction.

2. A process according to claim 1, wherein R^a is alkyl, aryl or acyl.

3. A process according to claim 1 or claim 2, wherein R^b is an acyl group.

4. A process according to claim 3, wherein OR^b is an ester group selected from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, p-nitrobenzoate, phthalate or succinate.

5. A process according to claim 1, wherein both R^a and R^b are acyl groups.

6. A process according to claim 5, wherein OR^a and OR^b are ester groups independently selected from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, p-nitrobenzoate, phthalate or succinate.

7. A process according to claim 6, wherein OR^a and OR^b are diphenylacetate.

8. A process according to any one of the preceding claims, wherein R^c, R^d and R^e are methyl.

9. A process according to any one of the preceding claims, wherein R^1 is OR" wherein R" is H, alkyl, substituted alkyl, acyl or silyl.

10. A process according to claim 9, wherein R^1 is OH.

11. A process according to any one of the preceding claims, wherein R^2 and R^4 are H.

12. A process according to any one of the preceding claims, wherein R^3 is C_5H_{11}.

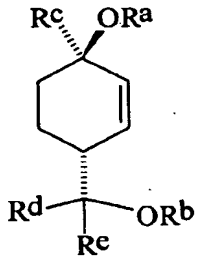
13. A process according to any one of the preceding claims, wherein compound A is Δ^9-THC, compound B is an ether or ester of (+)-*p*-menth-2-ene-1,8-diol and compound C is olivetol.

14. A process according to any one of the preceding claims, wherein the reaction of compound B with compound C is carried out in the presence of an acid catalyst.

15. A process according to claim 14, wherein the acid catalyst is nonmetallic.

16. A process according to claim 14 or claim 15, wherein 0.1-1.5 equivalents of acid are used.

17. A compound, represented by structure B,



Compound B

wherein OR^a and OR^b are independently chosen from acetate, propionate, butyrate, trimethylacetate, phenylacetate, phenoxyacetate, diphenylacetate, benzoate, *p*-nitrobenzoate, phthalate and succinate (provided that only one of OR^a and OR^b is acetate), and R^c, R^d and R^e are independently H, alkyl, or substituted alkyl.

18. A compound according to claim 17, wherein OR^a and OR^b are diphenylacetate.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/02159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/80

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	T.KAMETANI: "STEREOSELECTIVE CYCLISATION" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., vol. 3, 1981, pages 756-760, XP002210936 CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 0300-922X page 756	17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2002	09/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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PCT/GB 02/02159

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